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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,209	01/16/2001	James E. Hildreth	JHU1290-7	5480

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EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	**PAPER NUMBER**
1645	9

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/761,209	Hildreth
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 8-17 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 8-17 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed July 9, 2002 (Paper Number 7) has been received and entered. Claims 8-17 remain pending in the instant application.

Claim Rejections - 35 USC § 112

1. The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant's are asserting that the present invention is a passive immunization method, and that methods of passive immunization are well known in the art. Applicant's further point out that Fahey et al set forth that "80% or more of HIV individuals have antibodies capable of blocking gp160 binding to CD4 cells in vitro." Applicant's further assert that the present invention is distinguishable from Fahey et al in that the present invention suppresses intercellular leukocyte adhesion and therefore, can prevent an immune response.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the teachings of Fahey et al.

First, Applicant's are asserting that the present invention is a passive immunization method, and that methods of passive immunization are well known in the art. While this

statement is true, the claim is directed to a method of ameliorating a disorder wherein the disorder is HIV. Those of skill in the art recognize that there is no passive antibody based therapy which can ameliorate HIV. This position is clearly set forth by Fahey et al (Clin. Exp. Immunol. Vol. 88, pp 1-5, 1992) in which a summary of the results obtained in trials using **numerous different types** of immune-based therapies have not achieved success. (See table 1). Thus, while passive immunization for anti-venins are well know in the art, they are not commensurate in scope with immune-based therapies for HIV.

Second, Applicant's further point out that Fahey et al set forth that "80% or more of HIV individuals have antibodies capable of blocking gp160 binding to CD4 cells in vitro. However, again Applicant's are directed to Fahey et al summary which sets forth that numerous different types of immune-based therapy for HIV has not generated success.

Finally, Applicant's assert that the present invention is distinguishable from Fahey et al in that the present invention suppresses intercellular leukocyte adhesion and therefore, can prevent an immune response. However, the claim is directed to a method of ameliorating an immune response mediated disorder in an animal, wherein the disorder is HIV. Again, Fahey et al teach that antibody based therapies for HIV have been unsuccessful.

The claim is directed to methods of ameliorating an immune response mediated disorder in an animal wherein the disorder is AIDS, autoimmune disease, and graft rejection.

Applicant's specification contains insufficient guidance to one of skill in the art for the treatment of AIDS, autoimmune disease and graft rejection. The specification provides no description of critical parameters for administering antibodies in order to achieve a desired therapeutic outcome. General protocols for effective antibody-based treatment of AIDS, autoimmune disease, and graft rejection have not yet been established in the art. The specification does not describe what, if any, clinical changes or benefits are manifested as the result of monoclonal antibody-mediated individuals suffering from AIDS, autoimmune diseases or graft rejection such that one of skill in the art could determine the efficacy of the claimed invention. Undue experimentation would be required of one of skill in the art to practice the claimed methods relying only on the teachings of the instant specification for guidance in view of the current state of the art to which the invention pertains.

The obstacles to the development of therapeutic approaches with regard to the treatment of HIV-1 infection in humans are well documented in the scientific literature. Theses obstacles include the fact that the modes of viral transmission include virus-infected mononuclear cells which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, the existence of a latent form of the virus, the ability of the HIV-1 virus to hide in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus due to the blood-brain barrier, and the complexity and variation of the elaboration of the disease. The status of immunobased therapies in HIV infection and AIDS is summarized in a review article by Fahey *et al* (Clin. Exp. Immunol. Vol 88, pp 1-5, 1992), cited of interest, Fahey

et al teach that clinical benefit in trials using different approaches to immune-based therapies have not achieved a great deal of success. Table 1 on page 2 summarizes the results obtained in trials using numerous different types of immune-based therapies and teaches that antibody-based therapies involving the administration of immune serum gamma globulin or murine anti-gp160 monoclonal antibodies did not achieve clinical change or benefit. In view of the lack of working examples, and the lack of success which has been achieved to date in the use of immune-based therapies in general, and of antibody-based therapies in particular, for therapy of HIV-1 infection, one of skill in the art would be forced into undue experimentation to practice the broadly claimed invention.

For reasons of record in Paper Number 5, as well as the reasons set forth above this rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. The rejection of claims 8-9, 11, and 13-15 under 35 U.S.C. 102(e) as being anticipated by Arfors is maintained.

Applicant's are asserting that Arfors do not teach or suggest an immune response mediated disorder or of ameliorating an immune response mediated disorder.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the teachings of Arfors.

Arfors disclose of administering an antibody which binds to an epitope on the leukocyte adhesion receptor β-chain in order to prevent ischemia/reperfusion-induced tissue damage. (See column 2). Ischemia leads to necrosis, thus Arfors is ameliorating an immune response mediated disorder in that necrosis involves an immune response (inflammation) at the site of injury. Administration of the antibody to prevent necrosis or limit the amount of necrosis which takes place is thus deemed to be the amelioration of an immune response mediated disorder.

The claims are directed to a method of ameliorating an immune response mediated disorder in an animal which comprises: administering to the animal a therapeutically effective amount of an antibody, capable of suppressing intercellular leukocyte adhesion, wherein the antibody binds to an epitope on the leukocyte adhesion receptor β-chain.

Arfors (U.S. Patent Number 4,797,277) disclose of a method for treating mammalian organs suffering from ischemia in order to prevent ischemia/reperfusion-induced tissue damage,

which involves administering anti LAR-β chain-specific monoclonal antibody 60.3. (See column 2). The examples describe parenteral administration at a dose within the range specified in claim 15.

For reasons of record in Paper Number 5, as well as the reasons set forth above this rejection is maintained.

3. The rejection of claim 8 under 35 U.S.C. 102(b) as being anticipated by Vedder *et al* is maintained.

Applicant's assertions are the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Vedder *et al* (J. Clin. Invest. Vol. 81, pp 939-944, 1988) disclose of a method for reducing leukocyte-mediated organ injury by administering anti-CD18 monoclonal antibody 60.3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The rejection of claims 8-9, 11 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Arfors or Vedder *et al* in view of Springer *et al* is maintained.

Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Arfors and Vedder *et al* each teach that anti-CD18 monoclonal antibodies such as 60.3 inhibit leukocyte adherence functions and inhibit ischemia-reperfusion injury and speculate that these findings may be relevant to the therapy of many clinical disorders that result from ischemia and reperfusion including organ transplantation.

Neither Arfors or Vedder *et al* teach of LFA-1 or proteins capable of competing for receptors and of inhibiting cell to cell binding.

Springer *et al* (WO 88/06592) teach that the administration of LFA-1 or proteins capable of competing for receptors and of inhibiting cell to cell binding were recognized to have potential applicability for treatment of autoimmune diseases and graft rejection. (See page 12).

It would have been *prima facie* obvious to combine the teachings of the cited prior art and to administer anti-CD18 monoclonal antibodies such as Mab 60.3 which had been shown to inhibit cell adhesion, for the purpose of treating autoimmune diseases and graft rejection. One of ordinary skill in the art would have been motivated to do so in view of the teaching of Springer *et al* and Vedder *et al* as previously characterized.

5. Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arfors, Vedder *et al* and Springer *et al* as applied to claims 8-9, 11 and 13-15 above, and further in view of Hildreth *et al*.

Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2. Applicant's further assert that there is no motivation to combine the references in view that Vedder et al are not referring to an immunologic based rejection of an organ transplant but, instead, are describing injury that can occur upon reperfusion of the transplanted organ.

Applicant's are respectfully directed to the claim language which recites a method of ameliorating an immune response mediated disorder in an animal. As set forth above, ischemia of the organ can lead to necrosis of the tissue, which in turn results in an immune response (inflammation) at that site. It is this "immune disorder" which is being treated by the combination of the references.

Arfors, Vedder *et al* and Springer *et al* do not teach of the monoclonal antibody produced by ATCC HB X.

Hildreth *et al* (J. Immunology Vol. 134 pp 3272-3280, 1985) teach of the monoclonal antibody H52, which is the same antibody produced by the hybridoma cell line ATCC HB X. (Specification page 5).

It would have been *prima facie* obvious to substitute H52 into the methods suggested by the combined teachings of Arfors, Vedders *et al* and Springer *et al*. One of ordinary skill would have been motivated to do so in view of the teaching of Hildreth *et al* that Mab H52 had been shown to inhibit all T cell functions tested in a manner similar to the prior art Mab 60.3 which had been shown to be effective for inhibiting ischemia/reperfusion injury.

6. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arfors, Vedder *et al* and Springer *et al* as applied to claims 8-9, 11 and 13-15 above, and further in view of Pastan *et al*.

Arfors, Vedder *et al* and Springer *et al* do not teach of monoclonal antibodies labeled with a radioisotope, drug, lectin, or a toxin.

Applicant's assertions are essentially the same as those set forth above in paragraph 2, and have been addressed accordingly above in paragraph 2.

Pastan *et al* (Cell Vol. 47, pp 641-648, 1986) teach that the concept of using immunotoxins for the treatment of autoimmune disease, in autologous bone marrow transplantation and to improve organ graft survival. (See pages 645-6).

It would have been *prima facie* obvious to combine the teachings of the cited prior art and to produce conjugates comprising anti-LAR-β chain specific monoclonal antibodies and cytotoxic moieties and to use such conjugates in methods for treating autoimmune diseases and organ

transplantation. One of ordinary skill in the art would have been motivated to do so in view of the combined teachings of Pastan *et al*, Arfors *et al*, Vedder *et al*, and Springer *et al* as previously discussed.

Double Patenting

7. The rejection of claims 8-17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,888,508 is maintained.

It is noted that Applicant's have indicated a willingness to file a terminal disclaimer upon the indication of allowable subject matter. However until a terminal disclaimer is made of record this rejection is maintained.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

October 17, 2002